Surgical Management of Lung Cancer

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Abstract

Surgery serves an important role in the diagnosis, staging, and definitive management of non–small cell lung cancer (NSCLC). Resection is the primary mode of treatment for stage I and II NSCLC and an important component of the multimodality approach to stage IIIA disease. Standard resections include removal of the lobe involved with tumor and systematic evaluation of ipsilateral hilar and mediastinal lymph nodes. For early stage disease the evolving surgical treatment goals are aimed at decreasing morbidity and mortality through less invasive approaches including video-assisted thoracoscopic surgery and robotic approaches, and potentially decreasing the volume of lung removed for select patients with well-staged small peripheral tumors. For patients with locally advanced disease, ongoing research is focused on appropriately identifying patients who will most benefit from the addition of surgery to a multimodality regime and safely integrating resection with chemotherapy and radiotherapy.

Keywords
- non–small cell lung cancer
- surgery
- sublobar resection
- VATS
- robotic surgery
- multimodality therapy

Objectives: Upon completion of this article, the reader will be able to describe the indications for surgery in the treatment of non–small cell lung cancer.

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The surgical treatment of lung cancer is focused on accurate diagnosis and staging as well as definitive surgical treatment. Whereas small cell lung cancer is rarely treated by surgery, early stage patients with non–small cell lung cancer (NSCLC) are typically taken to surgery for resection for cure. Unfortunately, most NSCLC patients at the time of diagnosis have disease that has advanced beyond the point where local treatment such as surgical resection alone can provide cure, and these patients are treated in a multidisciplinary fashion. Recent advances in surgery for NSCLC have centered on less invasive approaches, in an effort to minimize the pain and complications common to these procedures.

Surgery for Early Stage NSCLC (Stage I and II)

Early stage NSCLC, defined as stage I and stage II, is usually treated with surgery as an initial modality. The current staging guidelines by the American Joint Committee on Cancer (AJCC) 7th edition TMN system define these as tumors up to 7 cm in size without mediastinal lymph node involvement, although ipsilateral hilar nodal disease is included. Tumor $>$7 cm are only considered to be stage II if there is no evidence of any lymph node disease.[1] A preoperative diagnosis of a suspicious pulmonary nodule is not required prior to definitive resection. There are two key aspects to surgery for early stage NSCLC: resection of the primary tumor and evaluation of draining lymph node basins in the ipsilateral hilum and mediastinum.

Systematic Mediastinal Lymph Node Evaluation

Evaluation of the draining lymph node basins provides information vital to the staging of lung cancer, and it is an integral part of surgery for NSCLC. Recent trials advocating the use of

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adjuvant chemotherapy to improve survival following complete resection of stage II and III NSCLC[2–4] has brought added importance to the hilar and mediastinal lymph node evaluation at surgery. Hilar and mediastinal lymph nodes are assigned stations as defined by the AJCC 7th staging edition for lung cancer, and they are essentially unchanged from the previous staging system.

Preoperative Lymph Node Evaluation

Cervical mediastinoscopy and anterior mediastinotomy (Chamberlain procedure) are procedures used to evaluate mediastinal (N2) lymph nodes for cancer involvement. As such, these procedures are frequently performed prior to definitive resection to help delineate which patients are early stage (stage I or II) from those with locally advanced disease (stage III). Both procedures require general anesthesia and can be performed either as a stand-alone operation, or in the setting of adequate pathology services, they may be used in the same sitting as a definitive resection.

Endoscopic techniques for transbronchial mediastinal lymph node sampling have emerged over the past decade. Blinded transbronchial techniques that are guided by computed tomography findings were described by Wang et al,[5] but the integration of live-action guidance with endobronchial ultrasound (EBUS) has increased diagnostic yield.[6–8] Although mediastinoscopy remains the gold standard for preresection mediastinal lymph node evaluation, EBUS has several advantages: (1) It is less invasive; (2) does not require general anesthesia; (3) can reach station 10 nodes in the hilum (which are typically not accessible at mediastinoscopy); and (4) does not produce mediastinal scarring, which facilitates repeat evaluation following chemotherapy and or radiotherapy.

The decision as to which patients require preoperative pathologic evaluation of mediastinal lymph nodes is individualized and typically based on the radiologic appearance of both the lymph nodes and the primary tumor. Mediastinal lymph nodes >1 cm in short axis or positive on fluorodeoxyglucose positron emission tomography (PET) are strongly recommended for biopsy. Other common indications for preoperative pathologic mediastinal lymph node evaluation include large tumors, central tumors, those with PET avidity in the ipsilateral hilum, or bilateral synchronous primary tumors.

Intraoperative Lymph Node Evaluation

During the definitive resection of a lung cancer, additional lymph node tissue is removed to assist in the cancer staging. All inter- and intralobar lymph nodes (stations 10 to 14) encountered during the hilar and fissural dissection are removed and sent for pathologic evaluation. A systematic evaluation of mediastinal lymph nodes is recommended and can be performed as a systematic sampling, where lymph nodes are biopsied at each of the ipsilateral mediastinal station (stations 2R, 4R, 7 and 9R on the right and levels 5, 6, 7 and 9L on the left), or by formal mediastinal lymphadenectomy where all associated nodes and soft tissue between anatomical landmarks are removed.

Some controversy has existed in the past regarding which of these approaches is most appropriate for patients undergoing lobectomy for cancer and if there is any survival or disease-free survival benefit for the more aggressive removal of lymphatic tissue. A recent randomized trial from the American College of Surgeons Oncology Group (ACOSOG Z0030) specifically addressed lymph node dissection versus sampling in >1000 early stage NSCLC patients undergoing resection; results failed to identify morbidity or survival differences between the two approaches.[9] However, the authors cautioned that the results did not apply to higher stage tumors that would be more prone to metastasize.

Lobectomy

Open Lobectomy

Results after anatomical lobectomy for early stage NSCLC are good. In the large ACOSOG Z0030 trial, disease-free survival at 5 years was 68% for resected early stage patients.[9] The completeness of resection, stage, and lymph node involvement are the primary predictors of survival after resection. Lung resections do carry significant risk, and up to 37% of patients may experience some form of postoperative complication.[10] The most common of these are minor and include atrial arrhythmia and prolonged air leak, but more serious complications including respiratory failure can occur and increase in frequency with decreased baseline pulmonary function (►**Table 1**). The operative mortality following lobectomy is reported to be 1 to 3%,[10,11] with pneumonia and respiratory failure as the overwhelming causative factors.

Video-Assisted Thoracoscopic Surgery Lobectomy

Video-assisted thoracoscopic surgery (VATS), like thoracotomy, is a surgical approach as opposed to a unique therapeutic intervention. The VATS approach to lobectomy for NSCLC typically involves two to four port sites and a 5- to 8-cm access incision. VATS is typically differentiated from a minithoracotomy by the lack of rib spreading and complete thoracoscopic visualization as opposed to visualizing the procedure directly through the incisions.[12] The rigid nature of the thoracic cavity is particularly well suited to scope-based surgical approaches as long as a pneumothorax can be maintained. The initial thoracoscopic procedures were reported in the early 20th century,[13] but widespread use of the VATS technique did not occur until the 1980s with improvement in video technology and the introduction of double-lumen endotracheal tubes to facilitate single lung ventilation. The first VATS lobectomy reports emerged in the 1990s, documenting safety and outlining technical aspects of the approach.[14–17] In the past decade, numerous large series have reported recurrence and survival data that are equivalent to open lobectomy.[18–21] VATS lobectomy is the same oncologic operation as the open approach, with removal of the pulmonary lobe containing the tumor with individual ligation of each of the bronchovascular structures and removal of hilar and mediastinal lymph nodes. Most large series of lobectomy by VATS describe a similar pattern of perioperative complications as the open approach but at reduced rates[18,19,22]

Table 1 Morbidity and mortality for lobectomy by thoracotomy

Study	*N*	Mortality (%)	Morbidity (%)						
			Pneumonia	Arrhythmia	Air leak >7 d	Hemorrhage	Empyema	Chylothorax	Recurrent laryngeal nerve injury
Harpole et al[58]	3516	5.2	11.3			2.9			
Allen et al[10]	1023	1.4	2.5	14.0	8.0	3.0	1.1	1.0	1.0
Licker et al[59]	1222	2.9	4.0		5.0		5.0		
Dominguez-Ventura et al[60]	379 (all ≥80 y of age)	6.3	4.0	21.0	7.0		1.0	1.0	2.0

(►**Table 2**). Although earlier recovery,[23,24] better quality of life,[23,24] increased delivery of adjuvant therapy,[25] and less impact on pulmonary function tests[26] and the immune system have been reported,[17] decreased pain and reduced length of stay appear to be the two most consistently reported advantages of VATS over open resections. It is currently estimated that <35% of lobectomies for NSCLC in the United States are performed by VATS,[12] but this number is increasing steadily. The inability to maintain single lung ventilation and dense pleural symphysis are the only definitive contraindication to VATS resections. Factors such as dense mediastinal scarring, central tumors, and tumors larger than the access incision are relative contraindications.

Robotic Lobectomy

Recent advances in robotic technology have benefited thoracic surgery. The advantages imparted by robotic technology for anatomical thoracic resections mirrors those of the VATS approach, namely smaller non-rib-spreading incisions resulting in less operative trauma for the patient. The theoretical benefits of robotic resections over a VATS approach include decreased pain at port sites, binocular visualization that allows for more precise dissection, and no requirement for an access incision. Additionally, given the totally portal nature of the procedure, carbon dioxide insufflation of the hemithorax can be used to further collapse the lung providing a larger working area. Finally, the advantage of using instruments that are jointed with increased range of motion (degrees of freedom) within the chest increases the ease of dissection.

The current approach for a robotic lobectomy consists of similar lateral decubitus positioning as the open or VATS approach. There are three or four access ports for the robot and one assistant port for stapling and retracting. The hilar and fissural dissection is similar to that of VATS and open approaches, although it takes places with a magnified three-dimensional view and precise movements afforded by the robotic equipment. The bronchovascular structures are dissected and individually divided with staplers, as with other approaches. One unique issue to the robot is that after the entire operation is conducted with small port incisions, the assistant's port frequently needs to be widened to permit egress of the specimen from the chest. Initial series of patients undergoing robotic lobectomy for NSCLC demonstrate safety, feasibility, and similar morbidity and mortality rates compared with open or VATS approaches.[27–29] However, the final determination on whether or not a given technique is feasible is the oncologic outcome. Although large longitudinal studies addressing long-term oncologic outcomes are needed, initial reports shows comparable stage-specific survival rates between the VATS and robotic approaches.[30,31] Cost comparisons between the robotic and VATS approaches is difficult due to the larger upfront cost of a robotic system; however, both approaches appear to have an overall cost benefit compared with open thoracotomy due to the significant decrease in length of hospital stay.[32]

Sublobar Resection

Lobectomy is the current standard care for lung cancer resections.[33] Sublobar resections refer to resections that

Table 2 Reported morbidity and mortality for VATS (video-assisted thoracoscopic) lobectomy

Study	*N*	Mortality (%)	Overall morbidity (%)
Yim et al[61]	214	0.5	22.0
Kaseda et al[62]	204	0.8	2.3
Roviaro et al[63]	171	0.6	8.7
McKenna et al[18]	1000	0.8	15.0
Onaitis et al[19]	500	1.0	15.0
Swanson et al[21]	180	0.6	21

remove less than an entire pulmonary lobe. These can be either anatomical segmentectomies or nonanatomical wedge resections. Early experience with sublobar resection for stage I NSCLC revealed comparable morbidity, reduced mortality,[34,35] and preserved pulmonary function compared with lobectomy.[36,37] Therefore, these procedures have always been offered as a compromise procedure for patients whose significant comorbidities or limited pulmonary function makes them unsuitable for lobectomy.

In 1995, the Lung Cancer Study Group (LCSG) reported the only prospective randomized study of lobectomy and limited pulmonary resections to delineate the impact of extent of resection on locoregional and distant recurrence rates for early stage disease. There was no significant difference in perioperative morbidity or mortality. However, there was a significant inverse correlation between extent of resection and locoregional recurrence (0.022 for lobectomy, 0.44 for segmentectomy, and 0.86 for wedge, reported in recurrence per year per person).[33] This trial established lobectomy as the gold standard for NSCLC resections. Recently, interest has arisen for sublobar resections as definitive treatment for small peripheral cancers. The impetus for this has been driven primarily by improvements in chest imaging that have resulted in increased detection of smaller, early stage, and more indolent lung cancers.

Because sublobar resections carry an increased risk for local recurrence compared with lobectomy, increased attention is placed on maintaining an adequate distance between the tumor and the resection margin. The concept is based on the need to clear local microscopic tumor extension. In a pathologic analysis of 70 NSCLC resection specimens, the degree of microscopic tumor extension varied by tumor histology, but 95% of observed microscopic tumor extension could be accounted for by a 6-mm margin in squamous cell carcinoma and an 8-mm margin in adenocarcinoma.[38] Ginsberg and Rubenstein, on behalf of the LCSG, recommended a 2-cm margin or a margin equivalent to the diameter of the tumor.[33] In a series of 87 patients undergoing sublobar resection for stage I NSCLC, El-Sherif and associates noted that tumor margins $\geq$1 cm were associated with a significantly lower recurrence rate when compared with margins <1 cm (8% versus 19%).[39] Sawabata and colleagues suggested margin distance greater than the maximum diameter of the tumor to minimize local recurrence risk.[40] Additional studies have demonstrated that a margin-to-tumor ratio <1 is associated with a significant increase in recurrence rates compared with ratios $\geq$1 (25.0% versus 6.2%).[41]

Segmentectomy

Segmentectomy is a technique that begins with a hilar dissection much like a formal lobectomy. The pulmonary artery branch to the segment of interest is dissected and individually ligated, as well as the bronchus to that segment. Once the bronchovascular hilar structures are divided, the anesthesiologist briefly inflates the lung and because the bronchus to the segment is transected, a line for pulmonary parenchymal transection is seen. The remainder of the procedure, including a systematic mediastinal lymph node sampling, continues as with lobectomy. Numerous single institution studies over the past decade have found no difference in survival or recurrence rates using anatomical segmentectomy compared with lobectomy[41–46] (►**Table 3**). Most of these studies were limited to tumors <3 cm in diameter.[47] and those with larger tumors report 50% higher local recurrence rate in stage IB tumors as compared with IA, highlighting the impact of tumor size on local recurrence.[48]

Wedge Resection

Wedge resections are nonanatomical resections that are typically performed by firing staplers across pulmonary parenchyma, and as such, many feel that they fall short of the accepted standard of care regarding surgical treatment of NSCLC. However, in selected patients, it may be the only surgical option. These include patients with significant comorbidities, those with small peripheral tumors that do not fall within segmental boundaries, and patient with metachronous primary NSCLCs facing multiple resections. When a nonanatomical wedge resection is used, the achievement of wide and negative pathologic margins is essential, and lymph node dissection should proceed as would be done with a more formal resection. Equally important, discussions preoperatively with the patient should focus on the limitations and increased risk of recurrence of the tumor with a lesser resection.

Surgery for Locally Advanced NSCLC (Stage IIIA)

Stage III lung cancer comprises a wide spectrum of locally advanced tumors.[1] Stage IIIB disease, which is typically defined by N3 disease (supraclavicular and contralateral

Table 3 Retrospective comparisons of survival following lobectomy and sublobar resections for non–small cell lung cancer

Study	*N*	Preoperative staging	Stage	Operative approach	Type of sublobar resection	Overall 5-y survival (%)	
						Lobectomy	Sublobar resection
Koike et al[43]	233	CT	IA	NR	81% segmentectomy; 19% wedge	90	89
Campione et al[44]	120	CT and bone scan	IA	100% thoracotomy	100% segmentectomy	65	62
Martin-Ucar et al[45]	34	CT	IA and IB	76% thoracotomy; 24% VATS	100% segmentectomy	64	70
Iwasaki et al[46]	86	CT	I, II, IIIA	77% thoracotomy; 23% VATS	100% extended segmentectomy	73	70
Kilic et al[41]	184	CT, selective PET, and mediastinoscopy	IA and IB	69% thoracotomy; 31% VATS	100% segmentectomy	47	46

Abbreviations: CT, computed tomography; NR, not reported; VATS, video-assisted thoracoscopic surgery; PET, positron emission tomography.

mediastinal or hilar lymph nodes), is not typically treated surgically. Stage IIIA disease presents in a very heterogeneous class of patients who are treated with a multimodality approach. The use of surgery in these treatment regimens is not universally accepted and should be evaluated on a case-by-case basis. A pretreatment tissue diagnosis is essential in this population because surgery is rarely the first mode of treatment. Ideally the tissue for diagnosis is obtained at a site that can also provide staging and therefore is generally focused on the mediastinal lymph nodes.

An important aspect of surgery for this stage is its safe integration with other therapies. Patients with stage IIIA NSCLC who can be considered for resection fall into three distinct classes: those with T3N1 tumors, those with T4 tumors without N2 involvement which are technically resectable, and those with nonbulky N2 disease and tumors up to T3. These patients require an individual assessment of resectability, and it should be emphasized that the interventions offered to these patients must be carefully tailored to the specific presentation of the patient.

T3N1 Disease

T3N1 disease refers to tumors that invade structures that can be routinely resected: chest wall, diaphragm, parietal pleura, and pericardium with hilar but no mediastinal lymph node involvement. Tumors within 2 cm of the carina are also included in this designation. These tumors are treated with surgery as an initial modality, and the goal is for an en bloc R0 resection, with incomplete resections carrying a much worse prognosis. Postoperatively, chemotherapy is recommended to reduce the risk of distant recurrence. Overall survival is acceptable and may be as high as 50% in some patients.[49] Postoperative radiation is reserved for patients in whom there is concern regarding the completeness of resection.

T4 Disease

T4 lesions are those with satellite lesions in a separate lobe and those that invade vital mediastinal structures, heart, great vessels, esophagus, carina, trachea, or vertebral body. When accompanied by N0 or N1 disease, these tumors are classified as stage IIIA, and if invasion is isolated to an individual structure they may be considered for surgery as the definitive treatment. The overall approach to these patients is an R0 resection in a manner that is technically feasible and safe. Tumors with invasion of the vertebral body require preoperative magnetic resonance imaging to evaluate for proximity to the spinal canal and nerve roots and frequently require orthopedic stabilization following resection.[50] Resections involving the trachea or carina have been described with acceptable outcomes in experienced hands.[51] Resection of T4 tumors invading the heart or great vessels has been described in smaller series, with up to 30 to 40% survival rates.[52] However, these operations frequently require cardiopulmonary bypass and should not be undertaken when complete resection is not possible.[53] Resections for T4 tumors almost always represent complex operations with increased risk for morbidity and mortality, and they should not be undertaken if there is evidence of mediastinal lymph node involvement.

Mediastinal Lymph Node Disease (N2)

Patients with N2 disease represent the largest subset of IIIA disease, and they have pathologically confirmed metastatic disease to the ipsilateral mediastinal nodes and/or subcarinal lymph nodes. These patients do very poorly with surgery as a sole treatment modality, with early studies showing 5-year survival rates <10% in patients with clinically apparent N2 disease.[54] This illustrates the concept of so-called bulky mediastinal disease, which carries a worse prognosis compared with metastatic disease that is not radiographically apparent prior to surgery.

Given the poor prognosis of N2 disease treated with surgery alone, therapeutic strategies have evolved to include multimodality approaches to this difficult patient group. A large 2008 meta-analysis showed significant benefit to postoperative chemotherapy in this population.[4] However, there was a 66% incidence of grade 3 or 4 adverse events, and 33% of the patients were not able to complete the adjuvant therapy. This called into question whether chemotherapy was more appropriate as neoadjuvant versus adjuvant therapy. The Southwest Oncology Group study (SWOG 8805) examined the impact of neoadjuvant chemoradiation and showed a 26% 3-year survival rate, and noted that survival was strongly correlated with completeness of resection.[55] More recent studies of trimodality therapy have shown encouraging 5-year survival rates of up to 50%.[56] In the recent intergroup trial 0139, which compared a trimodality treatment to definitive chemoradiotherapy for patients with IIIA disease, survival in the trimodality arm was diminished by high perioperative mortality among patients undergoing pneumonectomies and complex resections.[57] Lobectomy was better tolerated in this trial and associated with 5-year survival rates >40%, highlighting the potential benefit of this approach with careful patient selection and meticulous surgical technique. Several guiding principles appear to be consistent regarding the use of multimodality therapy for stage IIIA NSCLC: (1) neoadjuvant clearance of mediastinal disease confers a strong survival benefit, (2) patients who present with bulky mediastinal disease have a worse prognosis and may be more appropriate for definitive chemoradiotherapy for treatment, and (3) an R0 resection should be the absolute goal for any patient taken to surgery.

Conclusion

The surgical treatment for NSCLC is an ever-evolving field focused on treating a cancer that continues to carry high mortality. Multidisciplinary input is crucial in these patients who can frequently have significant medical comorbidities and complicated disease presentations and courses. Ongoing surgical research focuses on minimally invasive techniques that do not sacrifice oncologic efficacy and safe integration of surgery with other treatments. In spite of the efforts directed at the treatment of NSCLC, it still remains the largest cause of cancer-related deaths.

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